DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville MD 20852-1448

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CBER 98 -016

JUN 3 1998

WARNING LETTER

CERTIFIED - RETURN RECEIPT REQUESTED

Stuart Nielsen, Ph.D.
Allermed Laboratories, Inc.
7203 Convoy Court
San Diego, CA 92111

Dear Dr. Nielsen:

The Food and Drug Administration (FDA or the agency) conducted an inspection of Allermed Laboratories, Inc., located at 7203 Convoy Court, San Diego, California, on February 22 through February 27, 1998. The inspection revealed deviations from subchapter C, Part 211 and Subchapter F, Parts 600-680, Title 21, Code of Federal Regulations, (CFR), as follows:

1. Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile and to assure that such procedures include validation of any sterilization processes, in that the aseptic media fill procedure does not require or specify for simulated manipulations and activities such as mechanical repairs, dislodging jammed vials, employee breaks, replacement needles, etc.[21 CFR 211.113(b)].

2. Failure to establish appropriate time limits for the completion of each phase of production to assure the quality of the drug product, in that a time limit has not been established for the aseptic filling operation [21CFR 211.111].

3. Failure to clean, maintain, and sanitize equipment at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product [21 CFR 211.67(a) ; 211.113(b); and 600.11(b)]. For example:

    a. The cleaning of shared filling equipment used to aseptically fill licensed products and non-licensed food allergenic extracts is not validated.

b. The effectiveness of the disinfectant has not been established.

c. The interior surface of the [redacted] washer used to rinse vials prior to sterilization was observed to be corroded.

d. The teflon coating of the filter support plate of filtration housing [redacted] was observed to be deteriorated (flaking).

e. The pipette washer in the sterile glassware preparation area was observed to have standing water, debris and surface film.

f. Containers used to hold sterile water for injection (WFI) for final rinsing of vials are not sterilized or monitored for presence of microbes.

4. Failure to establish and/or follow written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to posses [21 CFR 211.100(a)]. For example:

a. The effectiveness of the sterile filtration processes has not been established.

b. No standard operating procedures exist for:
   i. monitoring of personnel performing aseptic filling operations
   ii. adverse event reporting
   iii. change control
   iv. internal and vendor audits
   v. city water monitoring

c. The written procedure entitled '[redacted] is not followed in that an investigation is not initiated when alert and action levels are reached.

d. The written procedure entitled [redacted] ' does not specify the maximum allowable size of a repair to HEPA filters before replacement.

e. The written procedure entitled [redacted] has not been updated to include the new cat and dog source material supplier.

5. Failure to routinely calibrate, inspect, or check automatic, mechanical, or electronic equipment used in the manufacture, processing, packaging, and holding of a drug product to assure proper performance, in that autoclave [redacted] (mycology

area), autoclave [redacted] extraction area), and autoclave #4 (microbiology area) have not been validated [21 CFR 211.68(a)].

6. Failure to establish separate or defined areas or other control systems for manufacturing and processing operations to prevent contamination or mix-ups, in that there is no assurance that proper segregation occurs between production and the mycology laboratory [21 CFR 211.42(c) and 211.42(c)(10)(iv)].

7. Failure to have written procedures for use of suitable cleaning and sanitizing agents designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products, in that the isopropyl alcohol used for sanitizing hands during aseptic filling operations is not sterile filtered [21 CFR 211.56(c)].

8. Failure to maintain buildings used in the manufacture, processing, packing, or holding of a drug product in a good state of repair, in that two holes were observed on the wall of the sterile glassware preparation area [21 CFR 211.58 and 600.11(a)].

9. Failure to test containers and closures for conformance with all appropriate written specifications, in that incoming containers and closures are not inspected for dimension specifications, cracks, particulates, and/or chips [21 CFR 211.84(d)(3)].

10. Failure to assure that container closure systems provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product, in that the integrity testing of the container closure system for allergenic products has not been performed [21 CFR 211.94(b) and 600.11(h)].

11. Failure to maintain adequate documentation of each significant step in batch production and control records [21 CFR 211.188(b) and 600.12(a)]. For example:

    a. The sterility test result for days 3 and 7 of incubation is not recorded. [21 CFR 610.12(a)]

    b. The result of the integrity test [redacted] on the filter used for grass pollen mixture lot Mp01199802 was not recorded in the batch production record nor the logbook per written procedure.

We have reviewed your March 24, 1998, written response which addresses the observations on the Form FDA 483 issued at the conclusion of the inspection. Corrective actions addressed in that letter may be referenced in your response to the Warning Letter, as appropriate. Although the majority of the responses appear to be adequate and will be verified upon reinspection, we have the following comments:

FDA-483 Item 1a

Your response indicates that studies to challenge the cleaning process with [redacted] is planned. Please provide the rationale for performing spiking studies with [redacted] and how this represents the most difficult to remove soiling of the product contact surfaces.

FDA-483 Item 1f

Upon completion of the final validation reports for autoclave [redacted], please submit the data for our review. In addition, please summarize the results of your evaluation of alternatives to the use of aluminum foil for wrapping items to be sterilized in the autoclaves.

FDA-483 Item 3

Your response states that there is no significant change in bioburden (microbes and molds) in the sterile production area related to the initiation of mold cultures in the mycology production area. Although the data provided do support a minimal impact, your study is limited in that it did not factor in the seasonal fluctuations in environmental mold level or specify the use of incubation conditions for environmental samples conducive to mold enumeration. Additionally, the ten day study described in the response is not sufficient to demonstrate the ability of your segregation systems to control the potential for mold cross contamination consistently over time. Please develop a plan to assess the segregation of mold culture activities from your common use production areas and submit this plan for review.

FDA-483 Item 10d

Your response indicates that a study to assess the pressure tanks used to hold WFI used in the glassware preparation area has been developed, including bioburden and pyrogen testing of the interior surfaces of the pressure vessels immediately prior to their use for dispensing WFI. This study is inadequate in that it does not (1) address the concern for potential microbial contamination of the WFI arising from low levels of microorganisms established on the water contact surfaces of the pressure vessels and (2) provide assurance of the ability of the pressure vessels to maintain and deliver WFI grade water consistently under standard operating procedures throughout the predefined use period of the pressure vessels.

A study to validate the ability of the pressure vessels to maintain the water quality attributes defined in the U.S. Pharmacopoeia which represents the worse case scenario based on written procedure for the use of these pressure vessels should be designed. The study should include (1) maximum holding time of the WFI in the pressure vessel; (2) testing of the WFI held for the maximum defined holding time in the pressure vessel for chemical, pyrogen, and microbial qualities; (3) an assessment of the longest period of time required for complete drying of the water contact surfaces inside the pressure vessels after use and draining of the dispensing vessel per written procedure; and (4) an assessment of the bioburden and endotoxin levels of residual water in the vessel near the end of the drying period. Please comment on this proposal or provide an alternative study for our

review. If you choose to perform this study as suggested, upon completion of the study, please submit the protocol, results, and report for review.

The above identified deviations are not intended to be an all inclusive list of deficiencies at your facility. It is your responsibility to exercise control of the establishment in all matters relating to compliance with all pertinent regulations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action includes license suspension and/or revocation, seizure and/or injunction. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the awards of contracts.

Please notify this office, in writing, within 15 working days of receipt of this letter of any additional steps you have taken to correct the noted violations and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

In addition, please contact Mary D. Davis-Lopez, Office of Compliance and Biologics Quality, Division of Case Management at (301) 827-6201 within 10 days of receipt of this letter to schedule a meeting with CBER to discuss your compliance status and this letter.

Your written response should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200N, Rockville, Maryland 20852-1448.

Sincerely,

Steven A. Masiello
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research